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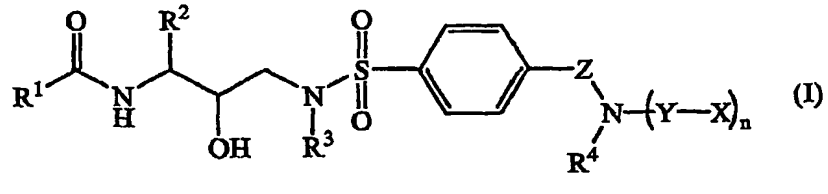
(54) Title: HIV PRODRUGS CLEAVABLE BY CD26



(I)

(57) Abstract: The present invention provides new prodrugs which are conjugates of a therapeutic compound and a peptide wherein the conjugate is cleavable by dipeptidyl-peptidases, more preferably by CD26, also known as DPPIV (dipeptidyl aminodipeptidase IV). The present prodrugs have the formula (I), the stereoisomeric forms and salts thereof, wherein n is I to 5; Y is proline, alanine, hydroxyproline, dihydroxyproline, thiazolidinecarboxylic acid (thioproline), dehydroproline, pipecolic acid (L-homoproline), azetidinecarboxylic acid, aziridinecarboxylic acid, glycine, serine, valine, leucine, isoleucine and threonine; X is selected from any amino acid in the D- or L-configuration; X and Y in each repeat of [Y-X] are chosen independently from one another and independently from other repeats; Z is a direct bond or a bivalent straight or branched saturated hydrocarbon group having from 1 to 4 carbon atoms; $R^1$ is an aryl, heteroaryl, aryloxy, heteroaryloxy, aryloxy$C_{1-4}$alkyl, heterocycloalkyloxy, heterocycloalkyl$C_{1-4}$akloxy, heteroaryloxy$C_{1-4}$alkyl, heteroaryl$C_{1-4}$alkyloxy; $R^2$ is aryl$C_{1-4}$alkyl; $R^3$ is $C_{1-10}$alkyl, $C_{2-6}$alkenyl or $C_{3-7}$cycloalkyl$C_{1-4}$alkyl; $R^4$ is hydrogen or $C_{1-4}$alkyl. The present invention furthermore provides the use of said prodrugs as medicines as well as a method of producing said prodrugs.

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B. FIELDS SEARCHED

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | WO 97/45117 A (PROTOTEK INC ; SMITH ROBERT E (US)) 4 December 1997 (1997-12-04) the whole document | 1-31 |
| A | WO 00/71571 A (BOEHRINGER SOHN INGELHEIM ; GARIN CHESA PILAR (DE); RETTIG WOLFGANG J) 30 November 2000 (2000-11-30) the whole document | |

-/--

[X] Further documents are listed in the continuation of box C.

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# INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/050753

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | BALAJTHY Z ET AL: "SYNTHESIS AND FUNCTIONAL EVALUATION OF A PEPTIDE DERIVATIVE OF 1-BETA-D-ARABINOFURANOSYLCYTOSINE" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 35, no. 18, 1992, pages 3344-3349, XP002939110 ISSN: 0022-2623 the whole document | |
| A | TROUET A ET AL: "Extracellularly tumor - activated prodrugs fo the selective chemotherapy of cancer: application to doxorubicin and preliminary in vitro and in vivo studies" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 61, no. 7, 1 April 2001 (2001-04-01), pages 2843-2846, XP002204750 ISSN: 0008-5472 the whole document | |
| A | US 5 962 216 A (BAURAIN ROGER ET AL) 5 October 1999 (1999-10-05) the whole document | |
| A | MASQUELIER M ET AL: "AMINO ACID AND DIPEPTIDE DERIVATIVES OF DAUNORUBICIN. 1. SYNTHESIS,PHYSICOCHEMICAL PROPERTIES, AND LYSOSOMAL DIGESTION" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 23, no. 11, 1980, pages 1166-1170, XP000914522 ISSN: 0022-2623 the whole document | |
| A | WO 99/67278 A (MANHART SUSANNE ; DEMUTH HANS ULRICH (DE); HOFFMANN TORSTEN (DE); PROB) 29 December 1999 (1999-12-29) the whole document | |
| A | ANAND BANMEET ET AL: "Novel dipeptide prodrugs of acyclovir for ocular herpes infections: Bioreversion, antiviral activity and transport across rabbit cornea." CURRENT EYE RESEARCH. 2003 MAR-APR, vol. 26, no. 3-4, March 2003 (2003-03), pages 151-163, XP009036464 ISSN: 0271-3683 the whole document | |

-/—

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/050753

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | AUGUSTYNS K ET AL: "THE UNIQUE PROPERTIES OF DIPEPTIDYL-PEPTIDASE IV (DPP IV/CD26) AND THE THERAPEUTIC POTENTIAL OF DPP IV INHIBITORS" CURRENT MEDICINAL CHEMISTRY, BENTHAM SCIENCE PUBLISHERS BV, BE, vol. 6, no. 4, 1999, pages 311-327, XP000870290 ISSN: 0929-8673 the whole document | |
| A | YARON A ET AL: "PROLINE-DEPENDENT STRUCTURAL AND BIOLOGICAL PROPERTIES OF PEPTIDES AND PROTEINS" CRITICAL REVIEWS IN BIOCHEMISTRY AND MOLECULAR BIOLOGY, CRC PRESS, BOCA RATON, FL, US, vol. 28, no. 1, 1993, pages 31-81, XP000925565 ISSN: 1040-9238 the whole document | |
| A | DE MEESTER I ET AL: "CD26, let it cut or cut it down" IMMUNOLOGY TODAY, ELSEVIER PUBLICATIONS, CAMBRIDGE, GB, vol. 20, no. 8, 1 August 1999 (1999-08-01), pages 367-375, XP004177365 ISSN: 0167-5699 cited in the application the whole document | |
| P,X | WO 03/048190 A (MITRA ASHIM K ; UNIV MISSOURI (US)) 12 June 2003 (2003-06-12) the whole document | 1,11-13, 25,26, 31,32, 43,44, 50,51, 54,55 |
| Y | WO 99/67254 A (UNIV ILLINOIS ; US HEALTH (US); ERICKSON JOHN W (US); GHOSH ARUN K (US) 29 December 1999 (1999-12-29) figure 5a | 1-31 |
| Y | BOONACKER EMIL ET AL: "The multifunctional or moonlighting protein CD26/DPPIV." EUROPEAN JOURNAL OF CELL BIOLOGY, vol. 82, no. 2, February 2003 (2003-02), pages 53-73, XP002302224 ISSN: 0171-9335 the whole document | 1-31 |

-/--

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/050753

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | OHTSUKI TAKASHI ET AL: "Good or evil: CD26 and HIV infection" JOURNAL OF DERMATOLOGICAL SCIENCE, vol. 22, no. 3, April 2000 (2000-04), pages 152-160, XP002302250 ISSN: 0923-1811 the whole document | 1-31 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/050753

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9745117 A | 04-12-1997 | AU 3224997 A | 05-01-1998 |
| | | CA 2256669 A1 | 04-12-1997 |
| | | CZ 9803893 A3 | 14-07-1999 |
| | | EP 0914123 A1 | 12-05-1999 |
| | | WO 9745117 A1 | 04-12-1997 |
| WO 0071571 A | 30-11-2000 | AU 6559100 A | 12-12-2000 |
| | | BG 106096 A | 31-05-2002 |
| | | BR 0010564 A | 19-02-2002 |
| | | CA 2369933 A1 | 30-11-2000 |
| | | CN 1374969 T | 16-10-2002 |
| | | CZ 20014097 A3 | 13-02-2002 |
| | | EE 200100600 A | 17-02-2003 |
| | | WO 0071571 A2 | 30-11-2000 |
| | | EP 1180116 A2 | 20-02-2002 |
| | | HU 0202367 A2 | 28-11-2002 |
| | | JP 2003500417 T | 07-01-2003 |
| | | NO 20015536 A | 10-01-2002 |
| | | NZ 516075 A | 26-03-2004 |
| | | PL 351680 A1 | 02-06-2003 |
| | | SK 16452001 A3 | 05-03-2002 |
| | | US 6613879 B1 | 02-09-2003 |
| | | ZA 200109151 A | 17-12-2002 |
| US 5962216 A | 05-10-1999 | BE 1008580 A3 | 04-06-1996 |
| | | BE 1008581 A3 | 04-06-1996 |
| | | AU 694546 B2 | 23-07-1998 |
| | | AU 3248695 A | 14-03-1996 |
| | | WO 9605863 A1 | 29-02-1996 |
| | | CA 2203622 A1 | 29-02-1996 |
| | | EP 0769967 A1 | 02-05-1997 |
| | | JP 10508291 T | 18-08-1998 |
| | | NO 970748 A | 10-04-1997 |
| | | NZ 291368 A | 29-04-1999 |
| | | US 2002160943 A1 | 31-10-2002 |
| | | US 6342480 B1 | 29-01-2002 |
| WO 9967278 A | 29-12-1999 | DE 19828113 A1 | 05-01-2000 |
| | | AU 766726 B2 | 23-10-2003 |
| | | AU 4900799 A | 10-01-2000 |
| | | BR 9911468 A | 20-03-2001 |
| | | CA 2335992 A1 | 29-12-1999 |
| | | CN 1306540 T | 01-08-2001 |
| | | WO 9967278 A1 | 29-12-1999 |
| | | EP 1087991 A1 | 04-04-2001 |
| | | HU 0102281 A2 | 28-11-2001 |
| | | JP 2003524591 T | 19-08-2003 |
| | | NO 20006484 A | 19-12-2000 |
| | | NZ 508722 A | 25-07-2003 |
| | | PL 345151 A1 | 03-12-2001 |
| | | RU 2226533 C2 | 10-04-2004 |
| | | US 2004171555 A1 | 02-09-2004 |
| | | US 2002049164 A1 | 25-04-2002 |
| WO 03048190 A | 12-06-2003 | WO 03048190 A2 | 12-06-2003 |
| WO 9967254 A | 29-12-1999 | AU 771780 B2 | 01-04-2004 |
| | | AU 4828099 A | 10-01-2000 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/050753

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9967254 A | | AU 4828199 A | 10-01-2000 |
| | | CA 2336160 A1 | 29-12-1999 |
| | | EP 1088098 A2 | 04-04-2001 |
| | | JP 2002518063 T | 25-06-2002 |
| | | WO 9967417 A2 | 29-12-1999 |
| | | WO 9967254 A2 | 29-12-1999 |